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SUBSTANCES

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Memorandum

Subject: Risk Assessment for Cocamide DEA (PC 224600).

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I. Executive Summary

This document provides a summary of information known about the active ingredient (a.i.), Cocamide Diethanolamine (Cocamide DEA), pending EPA registration by GML Industries, LLC for use in the end-use product, A NATUREZA® FLEA SHAMPOO for cats and dogs.

Cocamide DEA was previously registered by EPA as a bacteriostat, disinfectant, sanitizer, and fungicide; however, in the early 1990's all products were voluntarily canceled. This cancellation was not due to risk issues; presumably the registrants elected to remove the products from the market as a business decision.

The acute toxicity studies submitted to support this registration indicated that Cocamide DEA has low oral toxicity in rats (Toxicity Category IV; MRID 44445603), caused moderate eye irritation (Toxicity Category III; MRID 44445603), and slight skin irritation in rabbits (Toxicity Category IV; MRID 44445603). Two additional irritation studies with A NATUREZA® FLEA SHAMPOO (10% a.i.) demonstrated that the shampoo was slightly irritating (Toxicity Category IV) to the skin of treated rabbits (MRID 44445608) and was minimally irritating (Toxicity Category III) when instilled into eyes of rabbits (MRID 44445607). A safety study to evaluate a 2% Cocamide DEA

shampoo indicated that the product caused dermal irritation of an unspecified grade but was not a sensitizer. Except for dermal irritation, no toxicity endpoints were identified.

Through an internet search, the EPA became aware of a National Toxicology Program (NTP) study on Cocamide DEA. The NTP draft report indicated that Cocamide DEA caused renal and liver tumors in mice. The test material was nonmutagenic in *in vitro* Salmonella, mouse lymphoma, sister chromatid exchange, and chromosomal aberration assays (NTP, 2001), but in an *in vivo* micronucleus assay, positive results were reported in male and female mice that received dermal applications of Cocamide DEA for 14 weeks.

The Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) classified Cocamide DEA into the category, "**Likely to be carcinogenic to humans**," based on the occurrence of renal tumors in male mice and liver tumors in male and female mice reported by the NTP (2001). That Committee further recommended a linear low-dose extrapolation approach for the quantification of human cancer risk based on the tumor rate in the mouse suggesting the highest potency (unit risk or Q_1^*) in either sex. This approach is supported by the lack of mode of action data on Cocamide DEA and a concern for the mutagenicity of that test material in the *in vivo* mouse micronucleus assay. The unit risk, Q_1^* (mg/kg/day)⁻¹, of Cocamide DEA based upon female mouse liver adenoma, carcinoma and/or hepatoblastoma combined tumor rates (1.76×10^{-1} mg/kg/day⁻¹ in human equivalents) was used for the risk characterizations.

In the absence of exposure information specific to Cocamide DEA in the pet shampoo products considered in this assessment, standard assumptions and methods are used to estimate exposure for residential use of A Natureza® Pet Shampoos. The estimated cancer risk for Cocamide DEA is 2.5×10^{-2} for application of the shampoo and 5×10^{-4} for post-application, which exceeds Biopesticides and Pollution Prevention Division's (BPPD) level of concern ($>1 \times 10^{-6}$).

The toxicological database for Cocamide DEA is incomplete. There are no toxicity studies available that demonstrate no-observed-adverse-effect levels (NOAEL) for non-carcinogenic endpoints, and because there are studies that demonstrate a potential for the carcinogenicity of Cocamide DEA, additional data or waiver rationales are required in accordance with 40 CFR, §158.690(c). These studies would include subchronic, chronic, developmental and reproductive toxicity, and metabolism studies. In addition, exposure studies and/or more specific information on the conditions of use, use rates and other information providing more refined estimates of exposure would be useful for more realistic characterization of potential cancer risks.

(This risk assessment was peer reviewed by the Health Effects Division's Risk Assessment Review Committee on April 11, 2002.)

II. Overview

A. ACTIVE INGREDIENT IDENTITY

The new end-use product, A NATUREZA® FLEA SHAMPOO contains 10% Cocamide DEA (diethanolamides of the fatty acids of coconut oil) and [REDACTED]. The manufacturing process of the end-use product is a mixture of 10% active ingredient and [REDACTED]. The product is a shampoo used on dogs and cats to control or eliminate fleas.

B. USES

Each application of pet shampoo containing Cocamide DEA (10% active ingredient) kills living fleas by suffocation and dehydration, and repeated applications may be necessary to destroy fleas hatched from eggs already on the animal at treatment or acquired from the immediate environment subsequent to the initial application. The registrant recommends a three to four week treatment period with treatments repeated at intervals from 3 to 7 days as needed (see e-mail from Lynn James-Meyer dated 11/26/2001 to Sheryl Reilly, BPB). The shampoo is a liquid which is to be rubbed into the coat of the pet then rinsed off with water. The label does not specify a quantity to be applied.

C. REGULATORY HISTORY

On October 10, 1964, Cocamide DEA was registered as a bacteriostat, but the product was canceled on October 10, 1989 due to non-payment of the maintenance fee. On August 21, and October 25, 1972, Cocamide DEA was registered as a disinfectant, sanitizer and fungicide. However, on January 22, 1991 and then on November 12, 1993 the remaining Cocamide DEA products were canceled due to non-payment of the maintenance fee. Then on December 1, 1997, GML Industries, LLC applied for registration of this Cocamide DEA end-use pet shampoo product.

The registrant requested waivers from mammalian toxicity and ecological non-target effects data requirements based on low mammalian toxicity and a history of safe use of Cocamide DEA. The Agency agreed that no data other than manufacturing process and product chemistry plus the acute eye and dermal irritation studies were needed because of the relatively low-toxicity of this biopesticide as demonstrated by publicly available data.

A notice of receipt of the application for Cocamide DEA was published on April 27, 1998, in the Federal Register (63 FR 20629), with a 30-day comment period. No comments were received as a result of this publication.

D. FOOD CLEARANCES/TOLERANCES

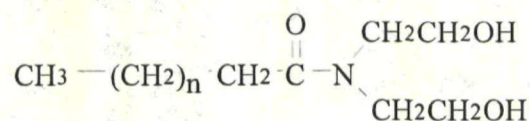
There are no food uses proposed for Cocamide DEA, so acute and chronic dietary risk assessments are not required.

III. Science Assessment

A. PHYSICAL AND CHEMICAL PROPERTIES ASSESSMENT

1. Product Identity

The biochemical pesticide Cocamide Diethanolamine (Cocamide-DEA; Pesticide Chemical Code 224600; CAS No. 68603-42-9) is composed of diethanolamides of the fatty acids found in coconut oil; free diethanolamine (CAS No. 111-42-2) is also present at 4-8.5% in the Cocamide DEA used in cosmetics (MRID 44445603) . Cocamide DEA is produced by condensation of diethanolamine with methyl esters of C₁₂-C₁₈ fatty acids (methyl laureate, myristate, palmitate, stearate, oleate, and linoleate; see the following structure).



$$n = 7, 9, 11, 13 \text{ or } 15$$

Synonyms for Cocamide DEA include:

Cocamide diethanolamine
diethanolamides of the fatty acids of coconut oil
coconut DEA
coconut diethanolamine

Chemical names include:

amides, coco, N,N-*bis*(hydroxyethyl)
N,N-*bis*(hydroxyethyl) coco amides
coconut oil acid, diethanolamine condensate

Cocamide-DEA is used in consumer products including cosmetics, soaps and shampoos and has been registered by BPPD as the active ingredient in pet shampoo (10% active ingredient) for use as needed against fleas.

2. Physical and Chemical Properties (Guideline Reference No. 151-17)

Chemistry data that support the registration of Cocamide DEA are summarized in Table 1, below.

Table 1a. Product chemistry data requirements for Cocamide DEA (Technical Grade a.i.)

Guideline No.	STUDY	RESULTS	MRID NO.
151-10	Product Identity and Composition	Product is identified as the commodity that is available in commerce.	44445601
151-15	Certification of limits	Limits listed in the CSF are adequate	CSF
151-16	Analytical Method	Described in 151-13, Analysis of Samples	44445606
151-17	PHYSICAL AND CHEMICAL PROPERTIES		44445602
151-17	Color	Clear amber	44445602
151-17	Odor	faint	44445602
151-17	Physical State	Liquid	44445602
151-17	Specific gravity	0.976	44445602
151-17	pH	9.5 - 10.5 (10% solution)	44445602
151-17	Flammability	Flash point at >200° F (93° C)	44445602
151-17	Viscosity	900 centipoise at 75° F	44445602
151-17	Storage Stability	Stable	44445602
151-17	Corrosion characteristics	Non-corrosive	44445602

Table 1b. Product chemistry data requirements for A Natureza® Flea Shampoo (end-use product)

Guideline No.	STUDY	RESULTS	MRID NO.
151-10	Product Identity and Composition	Product is identified as a commodity available in commerce.	44445604
151-17	PHYSICAL AND CHEMICAL PROPERTIES		44445605
151-17	Color	Clear amber	44445605
151-17	Odor	faint	44445605
151-17	Physical State	Liquid	44445605

Guideline No.	STUDY	RESULTS	MRID NO.
151-17	Specific gravity	0.976	44445605
151-17	pH	9.5 - 10.5 (10% solution)	44445605
151-17	Flammability	Flash point at >200° F (93° C)	44445605
151-17	Viscosity	900 centipoise at 75° F	44445605
151-17	Storage Stability	Stable	44445605
151-17	Corrosion characteristics	Non corrosive	44445605

3. Mode of Action

Cocamide DEA kills fleas by suffocation and dehydration.

B. HUMAN HEALTH ASSESSMENT

1. Toxicology Assessment

a. Acute Toxicity

The oral LD₅₀ for undiluted Cocamide DEA in rats was reported to be 12.2 g/kg (Toxicity Category IV; MRID 44445603), and limit tests (5 g/kg) with 10 to 12% formulations did not cause significant toxicity in acute studies. An eye irritation study (MRID 44445603) indicated that conjunctival irritation persisted for up to 3 days after instilling a 30% solution of Cocamide DEA in propylene glycol into the eyes of rabbits (Toxicity Category III). The irritation was no longer evident 4 days after treatment, and the test material was classified as a mild eye irritant. A skin irritation study in rabbits with the 30% Cocamide DEA in propylene glycol indicated the test material was a moderate skin irritant (MRID 44445603). Two additional irritation studies with A NATUREZA® FLEA SHAMPOO (10% a.i.) demonstrated that the shampoo was slightly irritating (Toxicity Category IV) to skin of treated rabbits (MRID 44445608) and was minimally irritating (Toxicity Category III) when instilled into eyes of rabbits (MRID 44445607).

Because Cocamide DEA is a moderate eye irritant and skin irritant, appropriate precautionary labeling is required. (See section, IV., B., 1. below.)

The published literature (MRID 44445603) described a safety and efficacy evaluation of a shampoo containing Cocamide DEA as follows:

One hundred four women participated in an in-use study to determine the safety and efficacy of a shampoo containing 2% Cocamide DEA. Each panelist was patch tested on the upper arm with 2% aqueous shampoo, 15 ppm (in water) of the shampoo's preservative system, and 5% shampoo fragrance in mineral oil. The three occlusive patches were applied and scored for irritation 48 h. later at the time of patch removal. The subjects were then instructed to shampoo daily with the test

product for 87 days. Ten days after final use of the shampoo, challenge patches were administered following the same procedure as the initial patches except the preservative concentration was increased to 50 ppm and an additional scoring for reactions was made 24 h. after patch removal. No reactions were observed to the preservative or fragrance patches. Eleven subjects reacted to the 2% shampoo initial patch; eight had mild erythema (1 + scores on a 0-4 scale), one had intense erythema (2 +), and two subjects had erythema and edema (3 +). Twenty-four subjects had irritation scores of 1+ (18/24), 2+ (3/24), and 3+ (3/24) 48 h. after challenge patch application of shampoo. Thirty subjects had 1+ (25/30) or 2+ (5/30) irritation scores at second challenge reading. All reactions were considered to be irritant in nature. The shampoo was an irritant but not a sensitizer.

b. Subchronic toxicity

i. Rabbits

A 28-day dermal toxicity study using Cocamide DEA formulated (1.9% a.i.) into a shaving cream was applied to the skin of groups of 4 male and 4 female rabbits at a rate of 500 mg/kg/application, 5 days/week (20 applications; MRID 44445603). Two animals of each sex had abraded skin and 2 had intact skin. The report noted moderate erythema, wrinkling, cracking and dry skin during the first week which continued throughout the study in treated animals. Skin irritation was observed at both intact and abraded sites. Blood glucose and serum alkaline phosphatase activities were found to be significantly higher in treated animals when compared with untreated control animals, and blood urea nitrogen values were significantly lower. No specific effects were attributed to treatment with the Cocamide DEA containing shaving cream.

ii. Rats

A 14-week dermal study was conducted in rats by the National Toxicology Program (NTP) to evaluate the cumulative toxic effects of repeated exposure to a form of Cocamide DEA and to determine the appropriate doses to be used in the 2-year rat carcinogenicity study. Groups of 10 male and 10 female rats received dermal applications of 0, 25, 50, 100, 200, or 400 mg active ingredient per kg body weight in ethanol (0, 30, 61, 121, 243, or 485 mg/mL ethanol). According to the report, all rats survived until the end of the study, and final mean body weights and body weight gains of 200 and 400 mg/kg males and females were significantly less than those of the vehicle controls. Nearly all 200 and 400 mg/kg males and females and two males and one female administered 100 mg/kg showed irritation of the skin at the site where test material was applied.

A minimal microcytic, normochromic, non-responsive anemia was noted in male and female rats at 100 mg/kg dose level and higher. Other effects included decreased cholesterol and triglyceride serum concentrations, a minimal increase in serum albumin concentration, increased total protein concentrations, minimal increases in urea nitrogen concentration, an increase in alanine aminotransferase activity, and increased alkaline phosphatase. Kidney weights of females administered 50 mg/kg or greater were significantly greater than those of the vehicle control group, and microscopic effects indicated signs of dermal irritation in both sexes and renal tubular regeneration in female rats. A no-observable-adverse-effect level (NOAEL) was not established in this study because some of the clinical chemistry parameters and dermal irritation were affected at all the doses tested. In addition, the report did not clearly indicate whether the animals were

exposed exclusively by the dermal route. However, this study was not intended to determine NOAELs or lowest-observable-effect levels (LOAEL).

iii. Mice

Groups of 10 male and 10 female mice received dermal applications of 0, 50, 100, 200, 400 or 800 mg Cocamide DEA per kg body weight in ethanol five days each week for 14 weeks in order to determine a dose range to be tested in the long-term carcinogenicity assay conducted by the NTP. The report indicated that all mice survived until the end of the study and that final mean body weights and body weight gains of dosed males and females were similar to those of the vehicle controls. The only treatment-related clinical finding was irritation of the skin at the site of application in all males and females administered 800 mg/kg.

The absolute and relative liver and kidney weights of 800 mg/kg males and females and the absolute and relative liver weights of 400 mg/kg females were significantly greater than those of the vehicle controls. The absolute and relative lung weights of 800 mg/kg females were also significantly greater than those of the vehicle controls.

Although this study was intended to define a dose range for use in the NTP's mouse carcinogenicity bioassay, a NOEL is suggested at 200 mg/kg/day and a LOAEL of 400 mg/kg/day is indicated on the basis of organ weight changes with other minimal indications of toxicity at higher doses.

c. Carcinogenicity Studies

i. Rats

Groups of 50 male and 50 female rats received dermal applications of 0, 50, or 100 mg Cocamide DEA per kg body weight in ethanol (0, 85, or 170 mg/mL ethanol) 5 days each week for 2 years.

Renal tubule neoplasms were reported in treated groups of both sexes. The NTP concluded that Cocamide DEA was not carcinogenic for male rats, but the evidence in females from the 50 mg/kg/day dose group was considered equivocal for kidney tumors.

The reported incidences of chronic nephropathy were similar between vehicle control and dosed groups of male and female rats, but in females the severity of this kidney lesion increased with dose. Among females, chronic active inflammation, epithelial hyperplasia and epithelial ulcer were observed in the forestomach. These findings were significantly increased at the 100 mg/kg level in females. The report noted that severity of these lesions was similar among all dose groups. The reported incidence of pancreatic acinar atrophy in 100 mg/kg male rats was significantly greater than that in the vehicle controls.

ii. Mice

Groups of 50 male and 50 female mice received dermal applications of 0, 100, or 200 mg/kg in ethanol (0, 50, or 100 mg/mL ethanol) five days each week for two years. Exposure to both dose levels significantly increased the incidences of hepatic tumors over that in the vehicle controls for male and female mice. In male and/or female mice, there were statistically significant ($p < 0.01$) dose-related increasing trends and significant increases ($p < 0.01$) by pair-wise comparisons with the controls (at ≥ 100 mg/kg/day) for hepatocellular adenomas, carcinomas (in females only), combined adenomas/carcinomas, hepatoblastomas (in males at 200 mg/kg/day only), and combined adenomas/ carcinomas/hepatoblastomas.

In male mice, there was a statistically significant increasing trend ($p < 0.01$) and a significant increase ($p < 0.05$ or 0.01) by pair-wise comparisons of the 200 mg/kg/day dose group with the controls for renal adenomas and combined adenomas/carcinomas. However, only the incidences of renal tubule adenomas and combined adenomas/carcinomas in male mice at 200 mg/kg/day were outside the historical control ranges. One 200 mg/kg female also had a renal tubule adenoma.

Several nonneoplastic lesions at the site of application were reported to be chemical related and they included epidermal hyperplasia, sebaceous gland hyperplasia, and hyperkeratosis in all dosed groups of both sexes. The incidences of these lesions were significantly greater than those in the vehicle control groups. The incidences of ulceration in 200 mg/kg males and inflammation and parakeratosis in 200 mg/kg females were also increased.

Increased incidences of follicular cell hyperplasia were also noted in thyroid glands of treated groups of males and females. The treated group incidences were significantly greater than those in the vehicle controls.

d. Mutagenicity

The NTP report stated that the genetic toxicity of Cocamide DEA was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells *in vitro*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in the peripheral blood of mice. Results of *in vitro* assays were described as uniformly negative. The test material did not induce mutations in *Salmonella typhimurium*, with or without metabolic activation. No increase in mutant mouse lymphoma cell colonies was observed after exposure to Cocamide DEA with or without S9 metabolic activation. A single positive response was noted in this test in the second trial conducted without activation but was not reproducible, so the test results overall were considered to be negative. In tests for induction of chromosomal damage, no increases in the frequencies of sister chromatid exchanges or chromosomal aberrations were observed in cultured CHO cells after incubation with Cocamide DEA with or without metabolic activation.

By contrast, positive results were reported in the micronucleus test in male and female mice *in vivo*. For this test, peripheral blood samples were obtained from dermally treated male and female

mice (0-800 mg/kg/day) at the end of the 14-week dermal study. These samples were used to prepare blood smears which were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in groups of five animals per sex per dose. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. After 14 weeks' treatment, significant increases in the frequencies of micronucleated NCEs were reported in peripheral blood of both male and female mice. Statistical analysis of the data showed positive trends for both data sets as well as significantly elevated micronucleus frequencies at the highest dose tested (800 mg/kg) in male and female mice.

2. Endpoint Selection

Based on available information and data (discussed above), no toxicity endpoints other than carcinogenicity were identified because the studies were intended to define dose ranges for further testing (subchronic dermal range finding studies in mice and rats), evaluate carcinogenic potential (the NTP bioassays in rats and mice) or to evaluate product safety (the human study with shampoo products or the rabbit dermal study with a shaving cream product).

3. Cancer Assessment

On July 25, 2001, the Cancer Assessment Review Committee (CARC) in the Health Effects Division (HED) evaluated the carcinogenic potential of Cocamide DEA. The Committee evaluated the dermal carcinogenicity studies in F344 rats and B6C3F₁ mice conducted by the National Toxicology Program (NTP).

In the 2-year rat study, 50 F344 rats/sex/dose received dermal applications of the test material at 0, 50, or 100 mg/kg/day in ethanol, 5 days a week for 2 years. In the 2-year mouse study, 50 B6C3F₁ mice/sex/group received test material by dermal applications at 0, 100, or 200 mg/kg/day in ethanol, 5 days a week for 2 years.

The CARC concluded that the evidence of carcinogenicity in F344/N female rats was equivocal and Cocamide DEA was carcinogenic to B6C3F₁ male and female mice based on the following findings:

- **In F344/N rats**, there was an increased incidence of renal tubule adenomas (12% vs 6% in controls) in males and a low incidence of carcinomas (4% vs 0% in controls) in females at 50 mg/kg/day but no increases in the occurrence of these tumors were observed at 100 mg/kg/day. A dose-related increased severity of chronic nephropathy was noted in females only. **The CARC agreed with NTP's assessment that the evidence of carcinogenicity in F344/N female rats was equivocal.** The dosing was considered to be adequate and not excessive based on the findings of dose-related increased severity of dermal toxicity (epidermal and sebaceous gland hyperplasia, hyperkeratosis, and parakeratosis). These signs of dermal irritation were supported by increased severity of skin lesions in a 14-week range-finding study. No treatment-

related effects were noted on the survival and body weights of either sex in the carcinogenicity study.

- **In B6C3F₁ male mice**, there was a statistically significant increasing trend ($p < 0.01$) and a significant increase ($p < 0.05$ or 0.01) by pair-wise comparisons of the 200 mg/kg/day dose group with the controls for renal tubule adenomas and combined adenomas/carcinomas. The combined incidence was driven by the adenomas and the incidence of adenomas was outside the historical control range. The incidence of carcinomas was within the historical controls range. In addition in both male and/or female mice, there were statistically significant ($p < 0.01$) dose-related increasing trends and significant increases ($p < 0.01$) by pair-wise comparisons with the controls (at ≥ 100 mg/kg/day) for hepatocellular adenomas, carcinomas (in females only), combined adenomas/carcinomas, hepatoblastomas (in males at 200 mg/kg/day only), and combined adenomas/ carcinomas/hepatoblastomas. The incidences of these tumors were outside the respective ranges for the historical controls. The dosing was considered to be adequate and not excessive based on increased (non significant) mortality in female mice in both dose groups late in the study and irritation of the skin. The body weights were comparable with the controls. **The CARC determined that the renal tumors are rare in male mice and concluded that the renal tumors in male mice and liver tumors in both male and female mice were treatment-related.**
- **Cocamide DEA** was nonmutagenic in *in vitro* Salmonella, mouse lymphoma, sister chromatid exchange, and chromosomal aberration assays. However, in an *in vivo* micronucleus assay positive results were reported in male and female mice that received dermal applications of 800 mg/kg/day for 14 weeks. **These results were reported in the same mouse strain as was used in the carcinogenicity study. The Committee concluded that a possible genotoxic mode of action in the carcinogenicity of Cocamide DEA cannot be ruled out.**
- Three NTP studies on structurally-related DEAs revealed that free DEA causes a pattern of renal and liver tumor incidences similar to cocamide DEA studies in mice. Liver tumors were also increased in female mice treated with lauric acid DEA condensate, a major component of coconut oil fatty acid DEA condensate but not with the oleic acid DEA condensate. The NTP correlated the free DEA levels in the four studies with the liver tumor incidences in female mice but not the renal tumors in male mice. **The CARC concluded that free DEA may have contributed to the induction of liver tumors observed in the mouse study, but an assessment of the carcinogenic potential of Cocamide DEA, which always contains some free DEA, should be based on results from the NTP studies with the material tested, i.e. DEA condensates of coconut oil fatty acids.**

According to the Agency's Draft Guidelines for Cancer Risk Assessment (July, 1999), the CARC classified Cocamide DEA into the category, **"Likely to be carcinogenic to humans,"** based on the occurrence of renal tumors in male mice and liver tumors in male and female mice. The Committee further recommended a linear low-dose extrapolation approach for the quantification

of human cancer risk based on the tumor in the mouse suggesting the highest potency (Q_1^*) in either sex. This approach is supported by the lack of mode of action data and a concern for the mutagenicity of Cocamide DEA.

4. Dose Response Assessment

A quantitative assessment of the tumor incidence data from studies with Cocamide DEA was conducted by HED (memorandum dated September 26, 2001 from L.L. Brunzman to R. Gardner, BPPD). All unit risks have been converted from animals to humans by use of the $3/4$'s scaling factor (Tox_Risk program, Version 3.5, K. Crump, 1994)¹. For the conversion to human equivalents, weights of 0.03 kg for the mouse and 70 kg for humans were used. The Q_1^* (mg/kg/day)⁻¹ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, the true value of the risk is unknown, and may be as low as zero. Because the data on Cocamide DEA supported the calculation of several unit risks, the highest of those derived from data on the active ingredient will be used to characterize risks.

The most potent unit risk, Q_1^* (mg/kg/day)⁻¹, of those calculated for Cocamide DEA and DEA, a contaminant of Commercial diethanolamide preparations, is that for DEA at 4.01×10^{-1} in human equivalents based on male mouse liver adenoma, carcinoma and/or hepatoblastoma combined tumor rates. The dose levels used from the 104-week dermal study were 0, 40, 80, and 160 mg/kg/day of DEA. The corresponding tumor rates were 39/50, 47/50, 50/50, and 49/50, respectively.

The unit risk, Q_1^* (mg/kg/day)⁻¹, of Cocamide DEA based upon male mouse kidney adenoma and/or carcinoma combined tumor rates is 7.50×10^{-3} in human equivalents. The dose levels used from the 104-week dermal study were 0, 100, and 200 mg/kg/day of Cocamide DEA. The corresponding tumor rates were 1/50, 1/50, and 9/50, respectively.

The unit risk, Q_1^* (mg/kg/day)⁻¹, of Cocamide DEA based upon male mouse liver adenoma and/or carcinoma combined tumor rates is 1.17×10^{-1} in human equivalents. The dose levels used from the 104-week dermal study were 0, 100, and 200 mg/kg/day of Cocamide DEA. The corresponding tumor rates were 28/50, 39/50, and 47/50, respectively.

The unit risk, Q_1^* (mg/kg/day)⁻¹, of Cocamide DEA based upon male mouse liver adenoma, carcinoma and hepatoblastoma combined tumor rates is 1.02×10^{-1} in human equivalents. The dose levels used from the 104-week dermal study were 0, 100, and 200 mg/kg/day of Cocamide DEA. The corresponding tumor rates were 29/50, 39/50, and 49/50, respectively.

The unit risk, Q_1^* (mg/kg/day)⁻¹, of Cocamide DEA based upon female mouse liver adenoma, carcinoma and/or hepatoblastoma combined tumor rates is 1.76×10^{-1} in human equivalents. The dose levels used from the 104-week dermal study were 0, 100, and 200 mg/kg/day of Cocamide DEA. The corresponding tumor rates were 33/50, 46/50, and 48/50, respectively.

The unit risk, Q_1^* (mg/kg/day)⁻¹, of DEA based upon female mouse liver adenoma, carcinoma and hepatoblastoma combined tumor rates could not be fit to the model due to the fact that all of the

dosed groups achieved 100% tumor rates. The dose levels used from the 104-week dermal study were 0, 40, 80, and 160 mg/kg/day of DEA. The corresponding tumor rates were 33/50, 50/50, 50/50, and 50/50, respectively.

5. Exposure Assessment

a. Dietary exposure

There are no food uses proposed for Cocamide DEA, so acute and chronic dietary risk assessments are not required and none were performed.

b. Residential exposure

i. Use Pattern

An unspecified quantity of the liquid Cocamide DEA pet shampoo (10% active ingredient) is rubbed into the dry coat of the dog or cat being treated, and then the animal is rinsed. Each application kills living fleas by suffocation and dehydration, and repeated applications are necessary to destroy fleas that hatch from eggs left in the coat after the initial application. Subsequent applications may also be needed to kill fleas acquired from the pet's immediate environment during the next few weeks. In order to disrupt the life cycle of the pest, a second application is recommended within 3 to 7 days after the first. Applications are to continue every 3-7 days for a period from 3 to 4 weeks in order to completely eradicate the pest. If the infestation persists, further treatments may be necessary.

ii. Exposure Estimates

In the absence of exposure information specific to Cocamide DEA in the pet shampoo products considered in this assessment, standard assumptions and methods¹ are used to estimate exposure for residential use of A Natureza® Pet Shampoos. Residential use is considered because there are no proposed label statements to indicate otherwise, and the exposure scenarios are limited to application of ready-to-use products, which contain 10% a.i. in this case. Ordinarily, a maximum application rate as stated on the label would be used, but in this case there is no quantitative rate indicated nor is there information on the amount of product in each container. Also, the only endpoint identifiable from existing toxicological data is the cancer endpoint suggested by the NTP rat and mouse bioassays, which would require the use of a typical application rate rather than the maximum label rate. Therefore, an exposure estimate was derived from an assumed use rate of one fluid ounce (28,350 mg) per application. In this case 10% of that amount (2835 mg) is Cocamide DEA and will be the estimated application rate. Higher use rates are more likely.

¹see *Standard Operating Procedures (SOPs) for Residential Exposure Assessments*, on the web at <http://www.epa.gov/scipoly/sap/1997/september/9sess3.htm>

Calculation of a daily dose is based on a single application event by a homeowner in a day. A homeowner is assumed to be exposed to 10% of the active ingredient applied during a single treatment or 2835 mg Cocamide DEA in a one fluid ounce application, and the weight of an average adult (male or female) is assumed to be 71.8 kg; the daily dose is $2835/71.8 = 39.5$ mg/kg/day when normalized for body weight.

For post-application exposure scenarios (exposure from contact with pets after treatment), the assumptions are that 20% of the Cocamide DEA applied is retained as dislodgeable residue on the pet (i.e., $2835 \times 0.2 = 567$ mg per fl. oz.) and 10% of that residue is assumed to be transferable to the individual in contact with the treated pet or 56.7 mg. It is typically assumed that residues do not dissipate on days subsequent to application because a specific level of pesticide is desirable to maintain activity against fleas, but this assumption may not be appropriate for Cocamide DEA since it suffocates and dessicates fleas and is mostly rinsed off after application. The post-application exposure estimates for Cocamide DEA are, therefore, limited to the day of treatment since there are no data on how much residue is left after rinsing of the pet. Using the assumed body weights of 71.8 kg for adults and 15 kg for toddlers 1-6 years old, estimated doses for post-application are 0.8 and 3.8 mg/kg per fl. oz., respectively.

Because the endpoint of concern is carcinogenicity, these exposure estimates for adults must be modified further to determine a lifetime average daily dose (LADD). As mentioned above, the use pattern indicated repeated use (every 3 days is assumed) for a maximum period of 4 weeks per year (approximately 9 applications in a month). Other assumptions used in this assessment include:

- a lifespan of 70 years for humans,
- treatment of a single pet for 10 years and,
- ownership of one pet per lifetime.

The LADD is calculated as follows:

$$\text{an annualized daily exposure} = (9 \text{ days}/365 \text{ days/year})(39.5 \text{ mg/kg/day}) = 1 \text{ mg/kg/day}$$

$$\text{LADD} = (\text{annualized daily exposure})(10 \text{ years exposure}/70 \text{ year lifetime})$$

$$= (1 \text{ mg/kg/day})(0.14) = 0.14 \text{ mg/kg/day for application}$$

Similar calculations for post-application exposure for adults provide an LADD of 0.003 mg/kg.

These calculations are based on limited circumstances, and it is likely that typical scenarios will result in higher exposures. For example, people may own more than one pet during their lives, a pet may require two or more treatment periods during a year, or one pet may be larger than another which would require more shampoo in one application. Without more specific information about the potential exposure to Cocamide DEA from the 10% shampoo products and typical patterns of

use, there can only be a low level of confidence in the lifetime average daily doses estimated in this exposure assessment.

It should be noted that the stated level of free DEA in the technical grade Cocamide DEA used for the products considered in this assessment is 0.5% so that LADDs for free DEA would be $(0.14 \text{ mg/kg/day})(5 \times 10^{-3}) = 7 \times 10^{-4} \text{ mg/kg/day}$ for application and $(3 \times 10^{-3} \text{ mg/kg/day})(5 \times 10^{-3}) = 1.5 \times 10^{-5} \text{ mg/kg/day}$ for post-application exposure.

iii. Risk Characterization

The most potent unit risk, Q_1^* (mg/kg/day)⁻¹, of those calculated for Cocamide DEA is 1.76×10^{-1} in human equivalents, based on the incidences of liver cell adenomas, carcinomas and hepatoblastomas combined in female mice. The most potent unit risk, Q_1^* (mg/kg/day)⁻¹, of those calculated for the free DEA contaminant of Cocamide DEA is 4×10^{-1} in human equivalents, based on male mouse liver adenomas, carcinomas and/or hepatoblastoma tumor rates. These values can be used to multiply the appropriate exposure estimates to characterize an upper bound cancer risk for the exposure scenario described above. **The estimated risk for application of Cocamide DEA (in one fl. oz. of flea shampoo) is $(1.4 \times 10^{-1} \text{ mg/kg/day})(1.76 \times 10^{-1} \text{ mg/kg/day}^{-1}) = 2.5 \times 10^{-2}$, and that for free DEA the estimated upper bound cancer risk would be $(7 \times 10^{-4})(4 \times 10^{-1}) = 2.8 \times 10^{-3}$. The estimated cancer risks for post-application exposure are $(3 \times 10^{-3})(1.76 \times 10^{-1}) = 5 \times 10^{-4}$ for Cocamide DEA and $(1.5 \times 10^{-5})(4 \times 10^{-1}) = 6 \times 10^{-6}$ for free DEA. For residential exposure, risks $> 1 \times 10^{-6}$ exceed BPPD's level of concern.**

It should be noted that the registrant provided commentary from public interest groups and a pre-publication manuscript raising concerns that the incidences of liver tumors in rats and mice may not be appropriate indicators of the carcinogenic potential of the impurity, free DEA. The comments also noted that Cocamide DEA, which contains free DEA as an impurity was not sufficient to support a conclusion about DEA's carcinogenic potential even though the NTP noted that the Cocamide DEA they tested contained 18% free DEA. However, no comments addressed the incidences of kidney adenomas and/or carcinomas combined in the male mouse which was observed in the study with Cocamide DEA. **The unit risk Q_1^* (mg/kg/day)⁻¹ based on the kidney tumor rate was 7.5×10^{-3} , and the upper bound on risk estimated for the shampoo use would be $(1.4 \times 10^{-1})(7.5 \times 10^{-3}) = 1 \times 10^{-3}$ for applicators and $(3 \times 10^{-3})(7.5 \times 10^{-3}) = 2.3 \times 10^{-5}$ for post-application exposure which exceeds the Agency's level of concern.**

These risks indicate the need for more specific information about potential exposure to Cocamide DEA from the pet shampoo use to more realistically characterize potential cancer risks to humans. In addition, the uncertainties regarding experimental conditions in the NTP studies (e.g., use of ethanol as a vehicle, the role of free DEA in tumor induction in the Cocamide DEA studies, results from other negative NTP carcinogenicity bioassays with lauric and oleic acid DEA condensates which are components of Cocamide DEA, etc.) need to be resolved with additional studies.

c. Drinking water exposure

No exposure is expected from an accumulation of Cocamide DEA in the aquatic environment due to the use pattern. Based on the available studies used in EPA's assessment of environmental risk, BPPD does not anticipate exposure of residues of this active ingredient in drinking water.

d. Sensitive subpopulations

Because there are no food uses, the Agency has concluded that there is no dietary hazard to the general population, including infants and children.

IV. DATA GAPS

The toxicological database is incomplete. There are no toxicity studies available to demonstrate no-observed-adverse-effect levels (NOAEL) for non-carcinogenic endpoints, and because there are studies demonstrating a potential for the carcinogenicity of Cocamide DEA additional data or waiver rationales are required in accordance with 40 CFR, §158.690(c). These studies would include subchronic, chronic, developmental and reproductive toxicity, and metabolism studies. In addition, exposure studies and/or more specific information on the conditions of use, use rates and other information providing more refined estimates of exposure would be useful for more realistic characterization of potential cancer risks.

V. REFERENCE

National Toxicology Program. 2001. Toxicology and Carcinogenesis Studies of Coconut Oil Acid Diethanolamine Condensate (CAS No. 68603-42-9) in F344/N Rats and B6C3F₁ Mice (Dermal Studies). (1997). National Toxicology Program Technical Report Series No. 479. dated January, 2001. NIH Publication No. 01-3969.